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SERIAL NUMBER	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
07/838,675	02/21/92	FALK	R PT-1039

EXAMINER	
MARTIN, I	

ART UNIT	PAPER NUMBER
1806	17

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DATE MAILED: 07/14/94

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☒ This application has been examined ☐ Responsive to communication filed on 4-20-94 ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), 0 days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☐ Notice of References Cited by Examiner, PTO-892.
2. ☐ Notice of Draftsman's Patent Drawing Review, PTO-948.
3. ☐ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____.

Part II SUMMARY OF ACTION

1. ☒ Claims 1-25 are pending in the application.
   Of the above, claims 1-5 and 21-25 are withdrawn from consideration.
2. ☐ Claims _____ have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☒ Claims 6-20 are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice of Draftsman's Patent Drawing Review, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____. has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed _____, has been ☐ approved; ☐ disapproved (see explanation).
12. ☐ Acknowledgement is made of the claim for priority under 35 U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____; filed on _____.
13. ☐ Since this application apppears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

EXAMINER'S ACTION

DETAILED ACTION

Election/Restriction

15. Applicant's election with traverse of Group II, claims 6-20, and species A, claims 6, 16 in Paper No. 16, 4-20-94 is acknowledged. The traversal is on the ground that Group I and Group II are not two patentably distinct inventions as evidenced by the Patent Office not requiring a similar restriction in copending application 07/838,674. This is not found persuasive because: (1) The use of the claimed product(composition) in cosmetics and/or the use of the process with other therapeutic agents as shown by Della Valle in U.S. Patent 4,851,521, clearly show Group I and Group II to be a patentably distinct product and process of use (MPEP § 806.05 (h)), 2)Examiner Nutter, who examined 07/838,674, also examined the instant application and drafted the original restriction requirement (see, Paper 6, 10-13-92), indicating that, he had determined that the two application should be handled differently. Each application is examined on its own individual merits. The requirement is still deemed proper and is therefore made FINAL. Claims 6-20 will be examined with the elected species. Claims 1-5 and 21-25 are withdrawn from further consideration by the examiner, 37 C.F.R. § 1.142(b) as being drawn to a nonelected invention.

Double Patenting

1. Claims 6-20 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 111-113, 162-165, 176-178, 228-231, and 244 of copending application Serial No.07/675,908, claims 57-58 of copending application Serial No.08/018,508, and claim 21 of copending application Serial No.08/018,754. Although the conflicting claims are not identical, they are not patentably distinct from each other because they are drawn to the same obvious invention of hyaluronic acid as a carrier for non-steroidal inflammatory agents in the treatment of cancer, for example skin cancer. The specific claims to the combination of hyaluronic acid, a non-steroidal anti-inflammatory drug with/or without various anti-neoplastic agents would have been obvious because one skilled in the art would select a combination of therapeutic agents most likely to be effective against a specific malignancy,taking into account cell type, body site, and patient history.

This is a *provisional* obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Oath/Declaration

The declaration is objected to because: Applicant has not complied with the requirements of 37 C.F.R. § 1.63(c), since the oath or declaration does not contain a complete claim for priority based on the Canadian application including serial number. Receipt is acknowledged of papers filed under 35 U.S.C. § 119 based on an application filed in Canada on 2-20-92. A new oath or declaration is required. Priority under 35 U.S.C. § 119 will be acknowledged once the new declaration claiming priority is received.

This application repeats a substantial portion of prior application Serial number 07/75,908, and adds claims and additional disclosure not contained in the original application. Should the applicant desire benefit of the filing date of the prior application, attention is directed to 35 U.S.C. § 120 and 37 C.F.R. § 1.78. The claim for filing under 35 U.S.C. § 120 should also be contained in the new declaration.

Claim Rejections - 35 USC § 101

16. 35 U.S.C. § 101 reads as follows:

> "Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title".

17. Claims 6-20 are rejected under 35 U.S.C. § 101 because the invention disclosed is inoperative and therefore lacks utility. The specification fails to establish the utility of the claimed topically applied pharmaceutical combination of hyaluronic acid and a non-steroidal anti-inflammatory agent in the treatment of basal cell carcinoma in a human patient. The applicant provides eight uncontrolled, unblinded, non-randomized case studies to assert the utility of the composition. Kelley et al, report the occurrence of spontaneous remission of basal cell carcinoma, see 892. The specification fails to establish that the remission incidence observed post treatment is greater than what would be expected spontaneously. Therefore it does not appear that the asserted utility of the claimed method for treating humans would be believable prima facie to persons of skill in the art in view of contemporary knowledge in the art. See MPEP 608.01(p).

Claim Rejections - 35 USC § 112

18. Claims 6-20 are rejected under 35 U.S.C. § 112, first paragraph, as the claimed invention is not described in such full, clear, concise and exact terms as to enable any person skilled in the art to make and use the same, and/or for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The disclosure is limited to the use of hyaluronic acid or sodium hyaluronate.

The instant application provides no description of how to make and/or use the various salts, and/or homologogues, analogues, derivatives, complexes, esters, fragments, and subunits of hyaluronic acid. It is improbable, because of the large number of compounds possible, that all of the broadly claimed derivatives of hyaluronic acid would be efficacious. This contention is supported by the applicants detailed description of the preferred hyaluronic formulations, including material obtained from commercial suppliers, see pages 34-49 of the specification.

Additionally Della Valle et al, teaches, in European Patent Applications 0265116 and 0197718 the adhesive and drug retarding effect of certain hyaluronic acid preparations, while Seifter et al in U.K. Patent 769,287, teaches the use of hyaluronic acid preparations for injection to enhance the spreading of therapeutic agents within the tissues, demonstrating the different hyaluronic acid preparations have greatly different properties, see 1449. The specification has not provided sufficient direction or guidance to one of skill in the art to properly select or administer these broadly claimed salts, and/or homologogues, analogues, derivatives, complexes, esters, fragments, and subunits of hyaluronic acid without undue experimentation.

19. Claims 11, 15, 20 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claims are indefinite in the recitation of "amount of hyaluronic acid or salt thereof in excess of 50-60mg per dosage, because the claims reads on any amount up to and including infinity.

Claim Rejections - 35 USC § 103

20. The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made. Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

21. Claims 6-20 are rejected under 35 U.S.C. § 103 as being unpatentable over Seifter et al, U.K. patent 769,287, in view of Schultz et al, U.S. patent 4,808,576, Miyazaki et al, Japanese

patent application 116678/88, and Della Valle et al, U.S. patent 4,736,024.

22. The claims are drawn to a method for treating a disease or condition with topical preparation of hyaluronic acid and a non-steroidal anti-inflammatory drug.

Seifter et al, teach the use of partially depolymerized hyaluronic acid as a carrier to facilitate the spreading of therapeutic agents into animal tissue. Seifter et al, also teach the careful control of the amount of depolymerization, because the physical characteristics of hyaluronic acid is dependent upon the degree to which the hyaluronic acid is depolymerized, i.e., the molecular weight. Seifter et al, determined the appropriate form of hyaluronic acid, for a given use, empirically by measuring the amount of time used for depolymerization, the molecular weight of the final polymer was not determined, see page 2, lines 105-130. Seifter et al, broadly teach that hyaluronic acid can be used to facilitate the spreading of a therapeutic agent, diagnostic agent, X-Ray contrast agent, anesthetic agent, and the use of hyaluronic acid for parental administration. Seifter states that the examples are illustrative and not intended to limit the invention, see page 2, column 1, lines 45-51. Seifter does not specifically teach the use of hyaluronic acid with non-steroidal anti-inflammatory agents.

Schultz et al, teach the relationship between the molecular weight of hyaluronic acid and the viscosity, showing the use of low molecular weight hyaluronic acid to facilitate its use for injection (column 5 lines 24-48) and more viscous solutions to facilitate transdermal administration (column 6, lines 1-33). Schultz et al, also teaches the topical use of hyaluronic acid with non-steroidal anti-inflammatory agents such as salicylates.

Miyazaki et al, teach the use of high molecular weight hyaluronic acid (560,000 to 1,240,000 daltons) as a carrier for controlled emission of therapeutic substances including anti-inflammatory agents (page 3, 2¶).

Della Valle et al, teach the use of hyaluronic acid as a carrier for pharmacologically active substances for topical ophthalmic use. Della Valle also states that hyaluronic acid preparations may be used in other applications such as dermatology or dentistry as a drug delivery system. Della Valle et al, teach the use of hyaluronic acid as a carrier for antibiotics and anti-inflammatory agents (column 3, lines 39-68) and anti-neoplastic agents (column 4, line 19).

From the teachings of the references, it is apparent that one of ordinary skill in the art at the time the invention was made would have been motivated to select and evaluate the efficacy of hyaluronic acid preparations of various molecular weights for topical use. Therefore it would have been obvious to

one skilled in the art to combine the teachings of Seifter et al. and Schultz et al. regarding the characteristics of various molecular weight preparations of hyaluronic acid with the teaching of Miyazaki et al. and Della Valle et al. to produce a multitude of different therapeutic agents. It is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

With regards to claims 11, 15, 20 drawn to hyaluronic acid preparations with molecular weights "less than about 750,000 daltons". Della Valle et al teaches the use of pharmaceutical preparations containing hyaluronic acid with a molecular weight ranging 50,000 to 730,000 daltons for topical and dermatological applications.

Schultz et al, teach the relationship between the molecular weight of hyaluronic acid and the viscosity, showing the use of more viscous solutions topical use (column 5 lines 24-48). From the teachings of the references, it is apparent that one of ordinary skill in the art at the time the invention was made would have been motivated to select and evaluate the efficacy of hyaluronic acid preparations selecting the appropriate molecular weight needed to facilitate the spread of therapeutic agents

administered by a particular route. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

23. No claim is allowed.

24. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dr. Martin, whose telephone number is (703) 305-6372. The examiner can normally be reached on Monday-Thursday from 8:00AM to 5:30PM. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, David Lacey can be reached on (703) 308-3535. The fax number for this Group is (703) 305-3230.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

7-14-94

Stephen J. Martin, Ph.D.

United States Patent and Trademark Office

DAVID L. LACEY
SUPERVISORY PATENT EXAMINER
GROUP 180
7/14/94